REMARKS

I. Status of Claims

Claims 1-7, 9, 11 and 14 are pending in this application. Claim 14 is currently withdrawn. Claims 8, 10, 12-13, and 15 are canceled. Claims 3-4, 6, 9, 11, and 14 have been amended. Support for the amendments to claims 9 may be found by way of example in originally filed claim 11. The amendments introduce no new subject matter.

II. Objection to the Abstract

The Examiner has objected to the abstract as allegedly not being on a separate sheet of paper. Applicants respectfully traverse as the abstract was on its own sheet of paper given that the rest of the disclosure on the page was not a figure, claim or part of the specification. However, to advance prosecution, a replacement abstract is submitted herewith. Applicants respectfully request that the abstract be entered at the end of the specification after the claims.

III. Objection to the Specification

The Examiner has objected to the specification for allegedly incorporating a list of patents, publications, or other information submitted for consideration into the specification. Applicants respectfully traverse. 37 CFR 1.98(b) sets forth the requirements for listing patents, publications and other disclosures in an information disclosure submitted to the USPTO for consideration. MPEP 609.04(a) states that the list that is being submitted for consideration in an information disclosure may not be incorporated into the specification, i.e., if the applicants want the USPTO to consider a reference, listing in the specification is not sufficient to comply with the rules of 37 CFR 1.98(b). Or put another way, a patent, publication or other disclosure listed in the specification but not on an information disclosure will not be considered by the USPTO. Applicants understand this and have submitted an information disclosure with references that they are aware of as being relevant to the pending claims in accordance with 37 CFR 1.56. Further, there is no requirement that all patents, publications and other disclosures referenced in a specification must be

submitted in an information disclosure statement. Therefore applicants respectfully request that the Examiner withdraw the objection to the specification.

IV. Claim Objections

The Examiner has objected to claim 4 as allegedly being in improper form as being multiply dependent upon a claim that is itself multiply dependent. To advance prosecution, Applicants have amended the claim to depend from claim 1. Applicant respectfully requests that the Examiner withdraw the objection to claim 4.

The Examiner has objected to claims 8 and 9 as failing to further limit the subject matter of the previous claim. To advance prosecution, Applicants have canceled claim 8 and amended claim 9 to include an additional element, "a second antigen." Applicant respectfully requests that the Examiner withdraw the objection to claims 8 and 9.

V. Rejections under 35 U.S.C. § 112, second paragraph

Claim 3 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention.

Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, applicants have amended claim 3 to recite "wherein the substitution is Glu to Asp." Applicants therefore respectfully request that the Examiner withdraw the rejection of claim 3 under 35 U.S.C. §112, second paragraph.

Claim 7 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention.

Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, applicants have amended claim 6

to depend from claim 5. Therefore now claim 6 is directed to a protein comprising a fragment and therefore the recitation of "the fragment" in claim 7 has proper antecedent support. Applicants therefore respectfully request that the Examiner withdraw the rejection of claim 7 under 35 U.S.C. §112, second paragraph.

VI. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-3, 5-9, and 11 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for any mutant *Neisseria meningitides* ADP-ribosylating protein or fragments thereof with any substitution at Glu-109 or Glu-111 or Glu-120.

Applicants respectfully traverse the rejection and its supporting remarks. As the Examiner has acknowledged, applicants have enabled Glu to Asp substitutions at any of Glu-109, Glu-111 or Glu-120 by virtue of having generated and tested each. The specification on page 35, lines 25-30, indicates that these three residues were identified as catalytic residues based upon homology to other ADP-ribosylating enzymes. The experiments performed by the inventors and disclosed herein demonstrate that the homology is in fact correct and these three are necessary catalytic residues in this enzyme. One of skill in the art would understand that catalytic residues are surface exposed residue necessary for the enzyme to perform its catalytic activity. The applicants work demonstrating that substitution of any one of these Glu residues with an Asp residue blocks catalytic activity while retaining or increasing the immunogenicity of the protein is extremely significant. Asp is very similar to Glu as it retains the negative charge of Glu while the side chain is only a single methyl group shorter. One of skill in the art would recognize that each of these three Glu residues are, as asserted by the inventors, three key residues in the catalysis performed by the enzyme. Since the catalytic residues are surface exposed, one of skill in the art would recognize that these three positions could each accommodate any of the other eighteen amino acid residues without significantly disturbing the fold of the enzyme and therefore maintaining the immunogenicity and adjuvant effect of the enzyme. One of skill in the art would further recognize that any of those eighteen other amino acid residues substituted at one of these three key catalytic residues would cause a similar or even greater reduction in the catalytic activity of the enzyme. If an Asp which has the same charge only almost the same size as Glu won't work, then certainly

insertion of any other residue besides a Glu won't work either. Thus, one of skill in the art would recognize based upon the disclosure of the present application that any of the eighteen other residues substituted at one of the three locations would provide the claimed functions and therefore the inventors have enabled the claims.

Even if one of the skill in the art could not predict that any of the other eighteen other residues would provide the claimed function, screening such would be an entirely routine procedure using molecular biology and enzymology techniques well known in the art and as disclosed in the working example provided on pages 33 through 37 as applied to the Glu to Asp substitutions. All one of skill in the art would need to do is generate each of the eighteen substitutions at the three different positions and screen them for activity, which requires generating a mere fifty-seven mutants (3*18).

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9 and 11 under U.S.C. §112, first paragraph, enablement.

VII. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1-3, 5-9, and 11 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks. Applicants have disclosed more that sufficient correlation between structure and function within the scope of the claims. The inventors identified the presently claimed enzyme's homology with other ADP-ribosylating proteins that others all overlooked (e.g., see Tettelin *et al.*, noted by the Examiner, who failed to assign the protein as an ADP-ribosylating protein). Such proteins are widely known and have been long studied, examples include diphtheria toxin, exotoxin A, cholera toxin, heat-labile enterotoxin and pertussis toxin (See page 1, lines 6-8 of the specification). Crystal structures are available for three of them (See page 1, line 20). Thus, there is a lot known about the structure and function of these proteins. The three Glu residues, 109, 111, and 120, identified by homology, are catalytic residues needed for the enzymatic activity. As discussed above, the inventors have

demonstrated how important these residues are for this catalytic activity as replacement of any one of them with a very similar residue Asp reduces the activity as claimed. Thus, the relationship between the structure and function is completely clear. The inventors have demonstrated that the structural requirements for function (i.e., the catalytic activity) are Glu residues at those positions. Furthermore, since these three residues are catalytic residues at the surface of the molecule, the surface exposure would allow substitution of these three Glu with any of the other nineteen residues. Since the very similar Asp would not support the catalytic activity, one of skill in the art would recognize that the other eighteen residues would similarly not support the catalytic activity and therefore would structurally support the claimed function of reduced activity. Furthermore, as the catalytic residues are surface exposed, any of the other eighteen residues would be accommodated without altering the immunogenicity. Thus, one of skill in the art would recognize that the applicants had possession of the invention as presently claimed due to the exquisitely exacting structural requirements of a Glu residue at each of the three positions being required for function based upon the lack of function when substituted with the very similar Asp residue.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9 and 11 under U.S.C. §112, first paragraph, written description.

VIII. Rejection under 35 U.S.C. § 102

Claims 1-3, 5-9, and 11 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Masignani *et al.* (WO 02/079242). Specifically, the Office Action alleges that Masignani *et al.* when given the broadest interpretation discloses the presently claimed invention.

Applicant respectfully traverses the rejection and its supporting remarks. 35 U.S.C. 102(e) applies when, "an application for patent, published under Section 122(b), by another filed in the United States ***before the invention by the applicant*** ... " Two of the three inventors of Masignani *et al.* are named as inventors of the present application. Thus, either the two presently named inventors invented any relevant subject matter in Masignani *et al.* or the third inventor on Masignani *et al.* should be added as an inventor to the presently application (and the applicants are

in the process of determining whether Rino Rappuoli should be added in light of the currently pending claim scope). In either case, Masignani *et al.* is not available as 35 U.S.C. 102(e) prior art.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9, and 11 under 35 U.S.C. 102(e).

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002103000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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